WITHANOLIDES IN THE VEGETABLE KINGDOM

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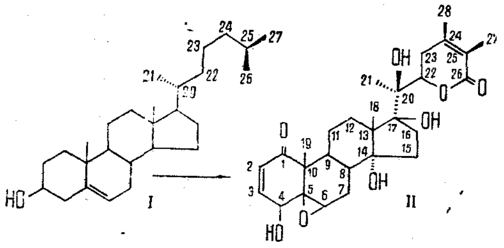
Investigations of recent years have confirmed that steroid compounds are obligatory components of all plants. Steroids take part in the formation of cell membranes and are found in the nuclei, chloroplasts, mitochondria, and other cell organelles.

The vegetable kingdom is capable of synthesizing all the main groups of steroid compounds characteristic of animals – sterols, cholic acids, corticoids, and sex hormones. However, in addition to these, in their vital activity plants elaborate a multiplicity of substances that are not characteristic of the animal world. In other words, so far as concerns structural diversity the steroids of vegetable origin have a considerably broader range than those of animal origin.



Two new classes of steroid compounds have been discovered in plants comparatively recently. One of them – the phytoecdysones – has been the subject of special reviews, [1, 2]. In the present paper we consider the other new group of steroids – the withanolides. In contrast to the ecdysones, which play the role of molting hormones in arthropods, the withanolides are characteristic solely of plants.

This peculiar group of phytosteroids obtained its name – withanolides – from the plant Withania somnifera Dun., in which they were first discovered [3]. Steroids of this group have been isolated in the individual state so far only from plants of the family Solanaceae (the genera Withania, Jaborosa, Acnistus, Dunalia, Datura, Nicandra, Physalis). The question of whether the withanolides can be considered as a chemotaxonomic characteristic confined to the family Solanaceae still remains open. No biological or chemical tests whatever that permit the error-free determination of the presence of steroids of the withanolide type in plants have been developed. They can be recognized mainly by spectral methods only after isolation in the individual, most frequently crystalline, state. Consequently, it is not excluded that withanolides will be found in future in other families of plants, as well.

On the other hand, in the family Solanaceae itself no phytosteroids of the group described have been found in such plants as henbane (Hyoscyamus), pepper (Capsicum), potato and eggplant (Solanum), and tomato (Lycopersicon).

On the biogenetic level, withanolides can be considered as derivatives of multiply oxidized cholesterol (I) with an additional methyl group at C-24 [4]. They all contain 28 carbon atoms of which nine are present in a side chain including a six-membered lactone ring, as in compounds (III-IX) found in Withania, Jaborosa, etc., or a pyran ring, as in the majority of nicandrins (X, XIX, XX). The number of oxygen-containing functions reaches eight (for example, 4β-hydroxywithanolide E, II) (See Scheme on following page.)

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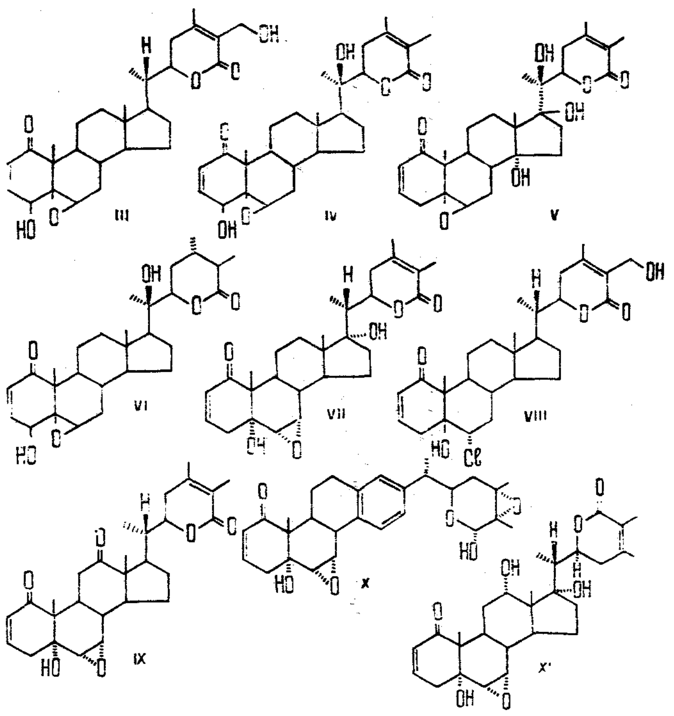
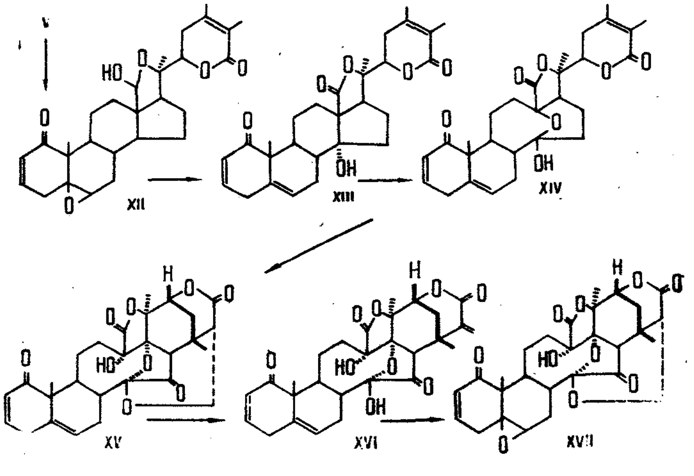


Scheme 1. Main types of withanolides.

Another feature of the withanolides is the presence in them, with a very few exceptions, of a Δ^2-1-keto grouping in ring A. Only two compounds – withanolides I and K – unlike the others, contain not an α,β- but a β,γ-unsaturated ketone grouping in ring A. It is interesting that some steroids of withanolide nature [21] and, in particular, jaborosolactones C (VIII) and E [23], which are isomeric with one another, include a chlorine atom (Scheme 1).

The physaline – a small group of compounds isolated exclusively from plants of the genus *Physalis* – must also be included among the withanolides. They also belong to the 28-C steroids and represent the most highly oxidized compounds, having a 13,14-seco-17,24-cyclo structure. The biogentic link of withanolide E (V) (it is found both in *Withania* [11] and in *Physalis* [51]) with $5\beta,6\beta$-epoxyphysalin B (XVII) through withaphysalins B (XII), A (XIII), and C (XIV) and physalins B (XV) and C (XVI) can easily be followed from Scheme 2.



Scheme 2. Biogenetic link of the withanolides and physalins.

The most widely used method of isolating the withanolides is methanol extraction [3, 22, 37]. The extract is evaporated, diluted with water, and re-extracted with hexane. The aqueous methanolic solution freed from fat

TABLE 1. Plants of the Family Solanaceae from which Individual Withanolides Have Been Isolated

Genus and species of plant	Plant organ	Name of the withanolide	Amount, % of the weight of the dry raw material	Literature
Withania somnifera Dun., chemotype I	Leaves	Withaferin A (III)	0,3[5] 0,2[7]	3,5–7,53
		Withanolide N		7
		Withanolide O		7
		Withanolide P		7
		27-Deoxywithaferin A		7
		27-Deoxy-14α-hydrowithaferin A	0,01	7,13
		27-Deoxy-17α-hydroxywithaferin A		7
		5α, 17α-Dihydroxy-1-oxo-6α, 7α-epoxy-20, 22R-witha-2,24-dienolide		7,9
Withania somnifera Dun., Chemotype II	Leaves	Withanolide D (IV)	0,05	7,10
		Withanolide G		7
		27-Hydroxywithanolide D		7
		14α-Hydroxywithanolide D		7
		17α-Hydroxywithanolide D		7
Withania somnifera Dun., chemotype (III)	Leaves	Withanolide E (V)	0,5	11,12
		Withanolide F	0,002	11,12
		Withanolide G	0,02	11,14
		Withanolide H	0,01	11,14
		Withanolide I	0,002	11,14
		Withanolide J	0,015	11,14
		Withanolide K	0,001	11,14
		Withanolide L	0,001	11
		Withanolide M	0,001	11,14
Withania somnifera Dun., South African population	Leaves	Withaferin A (III)	0,8	3
		Withanolide D (IV)	0,05	3
		27-Deoxywithaferin A	0,003	3
		4β, 20α(R)-Dihydroxy-1-oxo-5β, 6β-epoxywith-2-enolide (VI)	0,05	3
		4β-Hydroxy-1-oxo-5β, 6β-epoxywith-2-enolide	0,003	3
Withania somnifera Dun., Indian chemotype	Leaves	Withaferin A (III)	0,16	8
		27-Deoxywithaferin A		8
		27-Deoxy-14α -hydroxywithaferin A		8
		5α, 17α-Dihydroxy-1-oxo-6α, 7α-epoxy-22R-witha-2,24-dienolide (VII)	0,29	8,9
		5α; 17α-Dihydroxy-1-oxo-22R-witha-2,6,24-trienolide		8
		5α, 27-Dihydroxy-1-oxo-6α, 7α-epoxy-22R-witha-2,24-dienolide		8
		27-Deoxy-17α-hydroxywithaferin A		8
		17α, 27-Dihydroxy-1-oxo-22R-witha-2,5,24-trienolide		8
		7α, 27-Dihydroxy-1-oxo-22R-witha-2,5,24-trienolide		8
		1α, 3β, 5α-Trihydroxy-6α, 7α-epoxy-22R-with-24-enolide		8
		4β-Hydroxy-1-oxo-5β, 6β-epoxy-22R-witha-2,14,24-trienolide		8
Withania somnifera Dun.	Roots	5α, 20α-Dihydroxy-1-oxo-6α, 7α-epoxy-22R-witha-2,24-dienolide		15
Withania somnifera Dun.. F_3 genetic progeny from chemotypes I and III	Leaves	Withanolide Q	0,02	16
		Withanolide R		16
	Roots	Withaferin A (III)	0.15	17
		5α, 20α-Dihydroxy-1-oxo-6α, 7α-epoxy-22R-witha-2,24-dienolide		17
		5α, 27-Dihydroxy-1-oxo-6α, 7α-epoxywitha-2,24-dienolide		58

TABLE 1 (cont.)

Genus and species of plant	Plant organ	Name of the withanolide	Amount, % of the weight of the dry raw material	Literature
Withania ashwagandha	Roots	5α, 20α-Dihydroxy-1-oxo-6α, 7α-epoxy-22R-witha-2,24-dienolide		18
Withania aristata Pauq.	Epigeal part	Withaferin A (III)		19, 20
		2,3-Dihydrowithaferin A		20
		4β-Hydroxy-1-oxo-5β,6β-epoxy-22R-witha-2,14,24-trienolide		20
		4β,27-Dihydroxy-1-oxo-5β, 6β-epoxy-22R-witha-2,14,24-trienolide		20
		1α, 14α-Dihydroxy-22R-witha-5,24-dienolide		20
Withania frutescens Pauq.	Leaves	Withaferin A (III)		21
		2,3-Dihydrowithaferin A		21
		4β-27-Dihydroxy-1-oxo-5β-6β-epoxy-22R-witha-2,14,24-trienolide		21
		4β,17α,27-Trihydroxy-1-oxo-witha-2,5,24-trienolide		21
		4β,17α,27-Trihydroxy-1-oxo-22R-witha-5,24-dienolide		21
		6α-Chloro-4β,5β,27-trihydroxy-1-oxo-22R-witha-2,24-dienolide		21
Jaborosa integrifolia Lam.	Leaves	Jaborosalactone A	0,29	22,23
		Jaborosalactone B	0,4	22,23
		Jaborosalactone C (VIII)	0,08	23,24
		Jaborosalactone D	0,2	23,24
		Jaborosalactone E	0,08	23,24
Acnistus arborescens L. Schlecht	Leaves	Withaferin A (III)		25,26
		Withacnistin		26
Acnistus australis **Acnistus lorentzii** **Dunalia bracchiacan.**	Leaves	Withaferin A (III)		27
Acnistus australis (Dunalia australis) Griseb.	Leaves	4β,7β,20α(R)-Trihydroxy-1-oxowitha-2,5,24-trienolide	0,1	28
		4β, 7β, 20α(R)-Trihydroxyl-1-oxo-5β,6β-epoxywitha-2,24-dienoline	0,04	28
Dunalia australis Griseb.	Shoots	4β,7β,20α(R)-Trihydroxy-1-oxowitha-2,5,24-trienolide		29
Datura quercifolia HBK	Leaves	Daturalactone (XI)	0,06	30
		12-Oxowithanolide		31
Datura stramonium L.	Leaves	Daturalactone (XI)	0,03	32
Nicandra physaloides	Seeds	Nicandrenone (Nic-1) (X)		33
Nicandra physaloides, Indian population	Leaves	Nicandrenone (Nic-1 (X)	0,01	54
		Withanicandrin (IX)	[37] Main	34—37 36, 37
		Nic-2 (XX)	0,0006	38
		Nic-3 (XIX)	0,001	39,40
		Nic-7	0,003	39,40
		Nic-11 (XXI)		40
Nicandra physaloides, South African population	Leaves	Nic-1-lactone	Minor	41
	Epigeal part	Physalin A	0,02	42, 43
var. Franchetti		Physalin B (XV)	0,002	42—44
		Physalin C (XVI)		45
Physalis ixocarpa Brot.	Leaves	Withaphysacarpin		46
		Physalin B (XV)		46
Physalis minima	Leaves	Physalin B (XV)	0,4	47, 48
		5β,6β-Epoxyphysalin B (XVII)		48
		Withaphysalin A (XIII)		48
		Withaphysalin B (XII)	0,04	48
		Withaphysalin C (XIV)		48, 49
		Physalin D		50
Physalis peruviana L.	Leaves	Physalin A	0,01	47, 51
		Withanolide E (V)	0,2	51, 52
		4β-Hydroxywithanolide E (II)	0,2	51, 52
		2,3-Dihydrowithanolide E	0,01	51

and pigments is repeatedly extracted with ether and chloroform. Then the solvent is evaporated to dryness and is purified by chromatography on alumina.

Sometimes, the withanolides can be isolated by a fairly simple method: a benzene extract of the leaves of Datura quercifolia [30] merely on standing in the cold deposits crystals of daturalactone.

To isolated the physalins, the epigeal part of Physalis is extracted with hot water [43]. A chloroform extract from the aqueous solution contains the physalins, which can be isolated by fractional crystallization.

Iodine vapors are generally used to show up the spots on thin-layer chromatograms. However, in our view, it is more convenient to use a saturated chloroform solution of antimony tricholoride, since in this case spots of various shades – from pink to deep blue – are obtained.

A decision whether steroid lactones isolated in the individual state belong to the withanolide group is most conveniently made on the basis of the UV absorption spectrum. The two chromophores in the form of the α,β-unsaturated ketone group in ring A and the unsaturated lactone in the side chain, the effects of which are superposed on one another, give a strong maximum at 215-220 nm with a molar extinction coefficient ε of 18,000-20,000. In the IR spectrum, the bands of these chromophores appear separately at 1690 and 1660 cm^{-1}.

Steroids with a withanolide structure are present mainly in the leaves of plants of the family Solanaceae (Table 1). In individual cases, they have been found in the roots and fruit. The total amount of withanolides calculated on the dry weight of the plant rarely exeeds 0.5%, and in the majority of cases they are found in plants in amounts of hundredths and thousandths of a percentage part. Unfortunately, authors do not always give information on the amounts of the individual components, and it therefore does not appear possible to give an idea of the predominant accumulation of individual compounds.

Not all withanolides have been given trivial names (withanolides D-R, daturalactone, jaborosalactones A-E, nicandrins, physalins A-D, etc.); a considerable proportion of the minor compounds are denoted by rational and semirational names.

From chemotaxonomic points of view, the fact that a plant belongs to a particular genus or even to a definite species still does not mean that it will contain withanolides. In this respect, the group of compounds considered differs strongly from other plant steroids.

Although the capacity for producing withanolides is undoubtedly a hereditary characteristic, the impression is created that it was acquired by the plant at that stage of phylogenetic development when the main morphological characteristics determining the species affiliation had already come together and the newly acquired capacity did not appreciably affect them. In the examples given below, we shall encounter one of the phenomena of hereditary diversity: a species consists of types differing from one another.

The polymorphism of plants containing withanolides was first observed in Withania somnifera. It proved to be possible to divide plants of this species growing in the Near East (mainly on the territory of Israel) into three chemotypes according to the nature of the withanolides present in them [3, 4, 55]. Each of the chemotypes has a definite geographical region of distribution, but it is impossible to detect any differences of morphological nature whatever in the external appearance of the polymorphic groups. The types differ only in the nature of the steroid compounds of withanolide nature that they contain.

Chemotype I contains mainly withaferin A (III), together with a small amount of other compounds (see Table 1). The presence of withanolide D (20αR-hydroxy-27-deoxywithaferin A, IV) as the main component is characteristic for chemotype II. Chemotype III differs completely from chemotypes I and II in the structure of the steroid lactones that it contains. Quantitatively, withanolide E (V) predominates in it [11].

The structure of the withanolides isolated from chemotype I does not include an OH group at C-20, while in chemotype II all the compounds are hydroxylated at C-20. The substances from chemotype III contain OH groups both at C-17 and at C-20.

The constancy of the types is confirmed by the fact that plants grown from seed in a nursery have the same withanolide composition as those that were collected from the natural growth sites. It is interesting to observe that when chemotypes I and III were crossed, progeny were obtained the leaves of which contained mainly withanolide D (IV), which is characteristic of chemotype II and is never found in chemotypes I or III. At the same time, in the structural features of the other withanolides present in the leaves, the progeny of chemotypes I and III differed from the progeny of chemotype II. Analysis of plants of the second generation showed that, in agreement with the laws of genetics, segregation of the acquired characteristics had taken place and some of the individuals had reacquired the capacity for synthesizing the substances characteristic of chemotype I and others those of chemotype III.

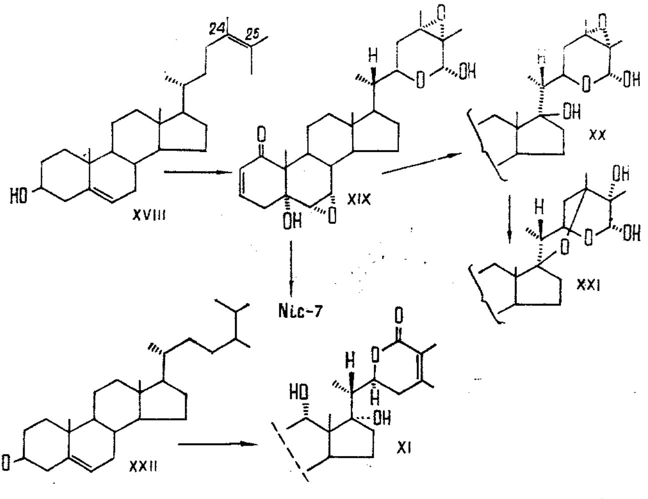
The plant Withania somnifera grown from seeds obtained from South Africa contained a set of withanolides differing from chemotypes I-III and formed a new type. Characteristic for this was the presence of, in addition to withaferin A and withanolide D, a considerable amount of withanolides with a saturated lactone ring in the side chain (in particular, 4β,20 αR-dihydroxy-1-oxo-5β,6β-epoxywith-2-enolide, VI).

Finally, for a population of plants found in the form of natural overgrowth in the southwestern part of India yet another complex of withanolides different from the others is characteristic [8] with a predominating content of steroid lactones with a 17α-hydroxy group. The most abundant of them is 5α,17α-dihydroxy-1-oxo-6α,7α-epoxy-22R-witha-2,24-dienolide (VII). In the literature, this chemotype has acquired the name of Indian I.

It is not only in W. somnifera that differences are observed in the composition of the steroid lactones according to the type of plant. Thus, the Indian population of Nicandra physaloides contains as the main substance withanicandrin (IX) – a compound of the type of withaferin A (III) with an unsaturated lactone ring – and nicandrenone (X) with a pyran ring in the side chain; the leaves of N. physaloides of Peruvian origin contain only nicandrenone (X) [36, 54].

Observations of the same type have been made by the authors of the present paper. The leaves of the plant Datura stramonium L., grown in Tashkent in the Botanical Garden of the Academy of Sciences of the Uzbek SSR, contain daturalactone (XI) and other withanolides (unfortunately, it has not been possible to establish the origin of the plant) [32]. The wild-growing variety of the same plant found in some regions of the Tashkent oblast and collected in various vegetation periods did not contain any steroid lactones at all in detectable amounts. No appreciable differences could be detected in the morphologies of the two types.

It has been stated above that the withanolides can be considered as derivatives of highly oxidized cholesterol (I). Although cholesterol contains 27 carbon atoms and the withanolides 28, this situation cannot be used as an objection, since the organism of higher and lower plants, unlike that of animals, has available enzyme systems that perform direct alkylation of the carbon atom in the side chain at position 24. Of the possible direct precursors of the withanolide lactones it is possible to point out at least four compounds that are present in the plant itself or have been found in tissue cultures of W. somnifera: 24-methyl-$\Delta^{24,25}$-dehydrocholesterol (XVIII), dihydroergosterol [56], campesterol (XXII), and 24-methylidenecholesterol [57]. Taking 24-methyldehydrocholesterol (XVIII) as a basis, Begley et al. [40] give the following hypothetical scheme of the biogenetic relationship of four nicandrins (Scheme 3).



Scheme 3. Hypothetical biogenetic relationship of sterols with withanolides.

The possibility of introducing into Nic-3 (XIX) two epoxide groups at the positions of the double bond appears to be a fact requiring no special investigation, since plants of the family Solanaceae that produce withanolides contain enxymes capable of epoxidizing isolated double bonds and double bonds forming part of allyl groups [41]. Oxidation at C-12 leads to the formation of Nic-7, differing from Nic-3 (XIX) by the presence of an additional ketone function at C-12. Passage to Nic-2 (XX) is possible via the 17β-hydroxylation of Nic-3. It is not excluded that Nic-11 (XXI) is formed from Nic-2 as the result of an intramolecular rearrangement of the 24,25-epoxy and 17β-hydroxy groups [38], as shown in the Scheme. A scheme of the biogenetic interrelationship of Nic-1 (nicandrenone, X), Nic-12, Nic-17, and Nic-10 has been suggested [35]. In all four nicandrins, ring D is aromatic.

In D. stramonium L., campesterol (XXII), which has been found in the leaves of this plant together with β-sitosterol and stigmasterol [32], may be a direct precursor of daturalactone (XI). As in the nicandrins, the double bond in ring B may serve as a convenient basis for the formation of the epoxy group (see Scheme 3).

The question of whether there are compounds of glycosidic nature among the withanolides still remains open. The only publication in this connection is due to Gonzalez et al. [20]. According to these authors, they succeeded in isolating from Withania aristata Pauq., together with a glycoside of β-sterol, a glycoside of 1α, 14α-dihydroxy-22R-witha-5,24-dienolide. However, no information whatever is given in the paper on the position of attachment of the sugar residue or on the physicochemical constants of the glycoside.

The chemistry of the withanolides is an intensively developing field of knowledge. It must be considered that in the coming years additional factual material will be obtained on the distribution of the withanolide steroids in the vegetable kingdom, on the structure of new compounds, and on their biogenesis and physiological activity.

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WITHANOLIDES – A NEW TYPE OF PHYTOSTEROIDS

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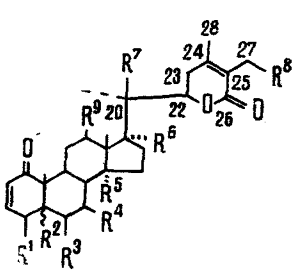
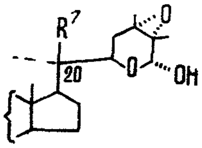
In recent years, to the types of steroids known previously [1, 2] a series of new ones isolated from natural sources of animal and vegetable origin has been added.

Some of the newly discovered types of steroid compounds are of great interest for their biological properties. Thus, compounds possessing a steroid skeleton of the ergostane type with a pyran ring in the side chain form a single biogenetic group which is found in plants of the family Solanaceae. New phytosteroids (about 60 compounds) have been isolated from Acnistus, Datura, Dunalia, Jaborosa, Withania, and Nicandra ph. and, accordingly, they have acquire the names of withanolides, jaborosalactones, withaphysalins, and nicandrins.





Biological Activity of the Withanolides

The enormous interest shown in the new class of phytosteroids, in the determination of their structure, and in the development of schemes of synthesis has been due to their biological activity. After the first report

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